Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/025277

International filing date: 05 August 2004 (05.08.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/493,109
Filing date: 05 August 2003 (05.08.2003)

Date of receipt at the International Bureau: 06 December 2004 (06.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1223724

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 23, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/493,109*
FILING DATE: *August 05, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/25277*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
and Acting Director of the U.S.
Patent and Trademark Office

Docket No.: 58664US002

Transmittal of Provisional Applicati n

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Inventor(s): David M. Hammerbeck, Houlton, WI
Cynthia A. Guy, Little Canada, MN;

Title: INFECTION PROPHYLAXIS USING IMMUNE RESPONSE MODIFIER COMPOUNDS

1. ☒ Enclosed is the above-identical new provisional application for patent under 35 USC § 111(b)(1). It includes:
   17 Pages of Text
   2 Sheets of Drawings

2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.

3. ☐ This invention was made under a contract with an agency of the U.S. Government:
   Agency: _____
   Contract No. _____

4. ☒ Correspondence Address: Christopher D. Gram
   Office of Intellectual Property Counsel
   3M Innovative Properties Company
   P.O. Box 33427
   St. Paul, Minnesota 55133-3427

5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.

6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.

7. ☒ Enclosed is a return receipt postcard.

16235 U.S. PTO
60/493109
08/05/03

Respectfully submitted,

Aug. 5, 2003
Date

By: Christopher D. Gram
Christopher D. Gram, Reg. No.: 43,643
Telephone No.: (651) 733-1507

Office of Intellectual Property Counsel
3M Innovative Properties Company
Facsimile No.: (651) 736-3833

Filing of Papers and Fees by Express Mailing

Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Date of Deposit	Express Mail Label No.
August 5, 2003	EV326638751US

☒ Customer Number for
Correspondenc Addr :

32692
PATENT TRADEMARK OFFICE

INFECTION PROPHYLAXIS USING IMMUNE RESPONSE MODIFIER COMPOUNDS

Background

Immune response modifiers ("IRMs") include compounds that possess potent immunomodulating activity including but not limited to antiviral and antitumor activity. Certain IRMs affect immune activity by modulating the production and secretion of cytokines. For example, cytokines that are induced by certain small molecule IRM compounds include but are not limited to Type I interferons, TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. Alternatively, certain IRM compounds can inhibit production and secretion of certain Th2 cytokines such as IL-4 and IL-5.

By stimulating certain aspects of the immune system, as well as suppressing other aspects, IRMs may be used to treat many diseases and conditions. For example, IRM compounds may be useful for treating viral diseases, neoplasias, fungal diseases, neoplastic diseases, parasitic diseases, atopic diseases, and opportunistic infections and tumors that occur after suppression of cell-mediated immunity. IRM compounds also may be useful for promoting healing of wounds and post-surgical scars. Specifically, but not exclusively, diseases that may be treated using IRM compounds include, but are not limited to, external genital and perianal warts caused by human papillomavirus, basal cell carcinoma, eczema, essential thrombocythaemia, hepatitis B, multiple sclerosis, neoplastic diseases, atopic dermatitis, asthma, allergies, psoriasis, rheumatoid arthritis, type I herpes simplex, and type II herpes simplex.

Certain formulations of a small molecule imidazoquinoline IRM compound have been shown to be useful for the therapeutic treatment of certain cancerous or pre-cancerous lesions (See, e.g., Geisse *et al.*, *J. Am. Acad. Dermatol.*, 47(3): 390-398 (2002); Shumack *et al.*, *Arch. Dermatol.*, 138: 1163-1171 (2002); U.S. Pat. No. 5,238,944; and WO 03/045391).

IRM compounds also can modulate humoral immunity by stimulating antibody production by B cells. Further, various IRMs have been shown to be useful as vaccine adjuvants (see, e.g., U.S. Pat. Nos. 6,083,505 and 6,406,705).

Certain IRM compounds are known to be agonists of at least one Toll-like receptor (TLR). For example, IRM compounds are known to be an agonists of TLR6, TLR7, TLR8, or some combination thereof. Also, for example, certain modified oligonucleotide IRM compounds are known to be agonists of TLR9.

Summary

It has been found that certain IRMs can be used to provide prophylaxis against an infectious agent when topically administered to the respiratory tract of a subject. Moreover, infection prophylaxis may be provided regardless of whether the IRM is administered before or after the subject is exposed to the infectious agent.

Accordingly, the present invention provides a method of providing prophylaxis to a subject against an infectious agent. The method includes topically administering to the respiratory tract of a subject an IRM compound in an amount effective to limit infection by the agent. In some embodiments, the IRM compound can be administered from about 72 hours prior to exposure to the infectious agent to about 72 hours after exposure to the infectious agent.

Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, claims and appended drawings. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

Detailed Description of Illustrative Embodiments of the Invention

The present invention relates to methods of providing prophylaxis against an infectious agent by topically administering an IRM compound to the respiratory system of a subject. In some embodiments of the present invention, the IRM compound is administered in a relatively limited dosing regimen that is specifically initiated upon actual, suspected, or anticipated possible exposure to an infectious agent. Therefore, certain methods of the present invention may be particularly suited for providing infection prophylaxis for those who have been, intend to be, or suspect that they may be exposed to an infectious agent.

For purposes of this invention, the following terms shall have the meanings set forth as follows:

"Exposure" of a subject to a pathogen refers to actual or anticipated contact between the subject and the pathogen. "Actual exposure" refers to exposure in fact, whether known or unknown. "Anticipated exposure" refers to any level of expected possibility of being exposed to a pathogen.

"Prophylaxis" refers to any degree of limiting an infection by an infectious agent including (a) preventing or limiting an initial infection, (b) preventing or limiting the spread of an existing infection, or both.

"Respiratory Tract" refers, generally, to the major structures and passages that permit or provide air flow between the environment and the lungs of a subject. "Upper Respiratory Tract" refers, generally, to the nasal cavity, paranasal sinuses, nasopharynx, oral cavity, pharynx, and larynx. "Lower Respiratory Tract" refers, generally, to the trachea and lungs, including the bronchi, bronchioles, and alveoli.

"Topical" refers to administering the IRM compound to a surface of the respiratory tract. Topical administration to the respiratory tract can occur via formulations including but not limited to an aerosol, a non-aerosol spray, a cream, an ointment, a gel, a lotion, a mouthwash, and the like.

The methods of the present invention can provide general prophylaxis against infection by an infectious agent. One feature of certain methods of the present invention is that topical administration of the IRM compound can provide infection prophylaxis against one or a plurality of known or unknown infectious agents. Knowledge or even suspicion of the identity of the particular infectious agent to which one has or might be exposed is not required. Accordingly, the methods of the present invention may be particularly useful when exposure to an infectious agent has occurred, is suspected to have occurred, or is anticipated, but the identity of the particular infectious agent is not known. Events in which the methods of the present invention thus may be particularly useful include, but are not limited to, outbreaks of new or previously unidentified infectious agents, biological warfare, bio-terrorism, and exposure to environments that can have a relatively large number of different infectious agents (e.g., health care clinics, daycare centers, and the like).

In certain embodiments, it may be possible to enhance infection prophylaxis against a particular infectious agent, if known, by combining administration of the IRM compound with separate or co-administration of one or more components of the infectious agent. However, infection prophylaxis using the methods of the present invention does not require such combinations or – as stated above - even knowledge of the identity of the infectious agent. Another feature of certain embodiments of the present invention is the ease and relatively limited discomfort associated with administration of the IRM compound. Topical administration to the respiratory tract can involve inhalation of an aerosol or non-aerosol formulation, the inhaled formulation being deposited on the surface of structures of the upper respiratory tract, the lower respiratory tract, or both. Alternatively, topical administration of the IRM compound to the respiratory tract may involve contacting a surface of the respiratory tract – typically, the upper respiratory tract – with a cream, gel, mouthwash, or the like. The formulation may be left in place following administration (e.g., a cream or gel applied to a surface of the oral or nasal cavity) or may be discarded (e.g., a mouthwash). Administration of the IRM compound can be minimally invasive, particularly when compared to subcutaneous, intramuscular, or transdermal vaccination.

Yet another feature of certain methods of the present invention is that administration of the IRM compound can be temporally connected to an exposure event, whether the exposure event has occurred, is suspected of having occurred, or is expected to occur. Moreover, infection prophylaxis can be provided without requiring administration of a prophylactic agent over weeks or months of treatment. For example, in some embodiments, infection prophylaxis can be provided by one or two doses of IRM compound administered about 72 hours or less before an anticipated exposure to an infectious agent. In some embodiments, infection prophylaxis can be provided by a single dose of IRM compound administered four hours before exposure to the infectious agent.

Alternatively, infection prophylaxis can be provided by administering the IRM compound after exposure to the infectious agent has occurred or is suspected to have occurred. For example, in some embodiments, infection prophylaxis can be provided by one or two doses of IRM compound administered about 72 hours or less after an actual or suspected exposure event. In certain embodiments, infection prophylaxis can be provided with a single dose of IRM compound provided within 24 hours of the exposure event. In

many embodiments, infection prophylaxis can be provided without requiring administration of a prophylactic or therapeutic agent over weeks or months of treatment.

In certain embodiments, administration of IRM compound before an anticipated exposure event may be combined with administration of IRM compound after an actual or suspected exposure event.

The features of certain embodiments of the present invention can be particularly desirable for some applications. For example, each of: (a) the temporal connection to an exposure event, (b) ease of administration, and (c) relatively short dosing regimens – alone and in various combinations – can increase the likelihood and extent of compliance, thereby increasing the efficacy of the prophylaxis.

As another example, the general infection prophylaxis conferred by administering IRM compound renders certain embodiments useful for providing infection prophylaxis even when the number and identity of infectious agent(s) is unknown. Thus, methods of the present invention may be particularly desirable in circumstances when, at the time when a standard vaccination would have to be given to provide infection prophylaxis, it is unclear to which, if any, infectious agents one may be exposed. Thus, infection prophylaxis using methods of the present invention can be provided on an "as needed" basis, thereby reducing the number of vaccinations administered unnecessarily.

Additionally, a single course of administering IRM compound may provide at least as great a scope - and in some cases, even greater scope - of infection prophylaxis as several vaccinations, with reduced costs (e.g., less developmental cost, one administration versus several), less discomfort, and without the inherent risk associated with standard vaccinations. All of the above factors may contribute to increased compliance compared to traditional vaccinations, which, in turn, may result in a higher percentage of individuals in a treated population having efficacious infection prophylaxis.

Infectious agents against which IRM compounds may provide infection prophylaxis using methods of the present invention include, but are not limited to: (a) viruses such as, for example, variola, HIV, CMV, VZV, rhinovirus, adenovirus, coronavirus, influenza, para-influenza, ebola, hepatitis B, and hepatitis C; (b) bacteria, such as those that can cause tuberculosis, anthrax, listeriosis, and leprosy; (c) other infectious agents such as prions and parasites (e.g., *Leishmania* spp.);

For example, certain methods of the present invention may be particularly useful for daycare or health care workers who have been or will be exposed to an infectious agent. Thus, certain methods of the present invention may secondarily reduce sick time taken by employees in certain industries.

As another example, certain methods of the present invention may be particularly useful for providing prophylaxis against biological warfare or bio-terrorism agents. Such methods may be employed by military personnel either (a) before an anticipated exposure to a biological warfare agent, (b) before entering an area where a biological warfare agent has previously been used, (c) or after a suspected or known exposure to a biological warfare agent. Certain methods of the present invention may be particularly useful in the event of exposure to a bio-terrorism agent. In some cases, the methods may be employed by emergency personnel including police, medical personnel, firefighters, and the like. In other cases, the methods may be employed by the general population or a subset of the general population. In either case, certain methods may provide infection prophylaxis when employed after either (a) exposure to a bio-terrorism agent, or (b) a warning that a bio-terrorism event may occur.

Suitable IRM Compounds

Immune response modifiers ("IRMs") include compounds that possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs modulate immune activity by modulating the production and secretion of cytokines. For example, certain IRM compounds can induce the production and secretion of cytokines such as, for example, Type I interferons, TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and/or MCP-1. As another example, certain IRM compounds can inhibit production and secretion of certain TH-2 cytokines, such as IL-4 and IL-5. Additionally, some IRM compounds are said to suppress IL-1 and TNF (U.S. Patent No. 6,518,265).

Certain IRM compounds are small organic molecules (e.g., molecular weight under about 1000 Daltons, preferably under about 500 Daltons, as opposed to large biologic protein, peptides, and the like) such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 4,988,815; 5,037,986; 5,175,296; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,367,076; 5,389,640; 5,395,937; 5,446,153; 5,482,936; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,039,969; 6,083,505; 6,110,929; 6,194,425; 6,245,776;

6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,545,016; 6,545,017; 6,558,951; and 6,573,273; European Patent 0 394 026; U.S. Patent Publication No. 2002/0055517; and International Patent Publication Nos. WO 01/74343; WO 02/46188; WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; WO 02/46749 WO 02/102377; WO 03/020889; WO 03/043572 and WO 03/045391.

Additional examples of small molecule IRMs include certain purine derivatives (such as those described in U.S. Patent Nos. 6,376,501, and 6,028,076), certain imidazoquinoline amide derivatives (such as those described in U.S. Patent No. 6,069,149), certain benzimidazole derivatives (such as those described in U.S. Patent 6,387,938), and certain derivatives of a 4-aminopyrimidine fused to a five membered nitrogen containing heterocyclic ring (such as adenine derivatives described in U. S. Patent Nos. 6,376,501; 6,028,076 and 6,329,381; and in WO 02/08595).

Other IRM compounds include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,194,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Some CpG-containing oligonucleotides can include synthetic immunomodulatory structural motifs such as those described, for example, in U.S. Pat. Nos. 6,426,334 and 6,476,000. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

The IRM compound may be any suitable IRM compound. In some embodiments of the present invention, the IRM compound may include a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring, or a 4-aminopyrimidine fused to a five membered nitrogen-containing heterocyclic ring. In some embodiments, suitable IRM compounds include but are not limited to the small molecule IRM compounds (e.g., molecular weight of less than about 1000 Daltons) described above. Certain small molecule IRM compounds - those having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring - include but are not limited to imidazoquinoline amines including but not limited to amide-substituted imidazoquinoline amines, sulfonamide-substituted imidazoquinoline amines, urea-substituted imidazoquinoline amines, aryl ether-substituted imidazoquinoline amines, heterocyclic ether-substituted imidazoquinoline amines, amido ether-substituted imidazoquinoline amines, sulfonamido ether-substituted imidazoquinoline amines, urea-substituted imidazoquinoline ethers, and

thioether-substituted imidazoquinoline amines; tetrahydroimidazoquinoline amines including but not limited to amide-substituted tetrahydroimidazoquinoline amines, sulfonamide-substituted tetrahydroimidazoquinoline amines, urea-substituted tetrahydroimidazoquinoline amines, aryl ether-substituted tetrahydroimidazoquinoline amines, heterocyclic ether-substituted tetrahydroimidazoquinoline amines, amido ether-substituted tetrahydroimidazoquinoline amines, sulfonamido ether-substituted tetrahydroimidazoquinoline amines, urea-substituted tetrahydroimidazoquinoline ethers, and thioether-substituted tetrahydroimidazoquinoline amines; imidazopyridine amines including but not limited to amide-substituted imidazopyridine amines, sulfonamido-substituted imidazopyridine amines, urea-substituted imidazopyridine amines; aryl ether-substituted imidazopyridine amines, heterocyclic ether-substituted imidazopyridine amines, amido ether-substituted imidazopyridine amines, sulfonamido ether-substituted imidazopyridine amines, urea-substituted imidazopyridine ethers, and thioether-substituted imidazopyridine amines;1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; and thiazolonaphthyridine amines. In certain embodiments, the IRM compound can be a sulfonamide-substituted imidazoquinoline amine. In certain specific embodiments, the IRM compound can be N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide..

Suitable IRM compounds also may include the purine derivatives, imidazoquinoline amide derivatives, benzimidazole derivatives, adenine derivatives, and oligonucleotide sequences described above. In some embodiments, the IRM compound may be a compound identified as an agonist of one or more TLRs. In some embodiments of the present invention, the IRM compound may be an agonist of at least one TLR, preferably an agonist of TLR6, TLR7, or TLR8. The IRM compound may, in some cases, be an agonist of TLR 9. In certain embodiments, the IRM compound is an agonist of at least both TLR7 and TLR8.

Formulations

The IRM compound may be provided in a formulation suitable for topical administration to the respiratory tract of a subject. The IRM compound may be provided in any suitable form including but not limited to a solution, a suspension, an emulsion, a dry powder, or any form of mixture. The IRM compound may be administered in formulation with any pharmaceutically acceptable excipient, carrier, or vehicle. The formulation may be administered in any conventional dosage form for topical delivery to a surface of the respiratory tract. Such dosage forms include but are not limited to an aerosol formulation, a non-aerosol spray, a cream, an ointment, a gel, a lotion, a mouthwash, and the like. Suitable aerosol formulations are described, for example, in U.S. Pat. No. 6,126,919. Alternative formulations are described, for example, in U.S. Pat. No. 5,238,944; EP 0 394 026; U.S. Pat. No. 6,365,166; and U.S. Pat. No. 6,245,776. The formulation may further include one or more additives including but not limited to adjuvants, penetration enhancers, colorants, fragrances, moisturizers, thickeners, and the like.

In some embodiments, the methods of the present invention include administering IRM compound to a subject in a formulation of, for example, from about 0.001% to about typically 10% (unless otherwise indicated, all percentages provided herein are weight/weight with respect to the total formulation) to the subject, although in some embodiments the IRM compound may be administered using a formulation that provides IRM compound in a concentration outside of this range. In certain embodiments, the method includes administering to a subject a formulation that includes from about 0.01% to about 1.0 % IRM compound, for example, a formulation that includes about 0.375% IRM compound.

Dosages

An amount of an IRM compound effective for providing infection prophylaxis is an amount sufficient to either prevent or limit (a) an initial infection, or (b) the spread of an existing infection, or both. One method of determining an amount effective for providing infection prophylaxis is to determine an amount effective to reduce – to a statistically significant extent - nasal or lung titers of the infectious agent 24 hours after the latter of: (a) exposure to the infectious agent, or (b) administration of the IRM compound.

The precise amount of IRM compound in a dose may vary according to factors known in the art including but not limited to the physical and chemical nature of the IRM compound, the nature of the carrier, the intended dosing regimen, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the IRM compound, the species to which the formulation is being administered, and the infectious agent or agents, if known, to which the subject has been or is expected to be exposed. Accordingly it is not practical to set forth generally the amount that constitutes an amount of IRM compound effective for providing infection prophylaxis for all possible applications. Those of ordinary skill in the art, however, can readily determine the appropriate amount with due consideration of such factors.

In some embodiments, the methods of the present invention include administering sufficient IRM compound to provide a dose of, for example, from about 100 ng/kg to about 50 mg/kg to the subject, although in some embodiments the methods may be performed by administering IRM compound in concentrations outside this range. In some of these embodiments, the method includes administering sufficient IRM compound to provide a dose of from about 10 μg/kg to about 5 mg/kg to the subject, for example, a dose of from about 100 μg/kg to about 1 mg/kg.

Dosing Regimen

The dosing regimen may depend at least in part on many factors known in the art including but not limited to the physical and chemical nature of the IRM compound, the nature of the carrier, the amount of IRM compound being administered, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the IRM compound, the species to which the formulation is being administered, and the infectious agent or agents, if known, to which the subject has been or is expected to be exposed. Accordingly it is not practical to set forth generally the dosing regimen effective to provide infection prophylaxis for all possible applications. Those of ordinary skill in the art, however, can readily determine the appropriate amount with due consideration of such factors.

In some embodiments of the invention, the IRM compound may be administered, for example, from once to about twelve times over the entire course of treatment, although in some embodiments the methods of the present invention may be performed by

administering the IRM compound at a frequency outside this range. In certain embodiments, the IRM compound may be administered from once to about four times over the entire course of treatment. In one particular embodiment, the IRM compound is administered once. In another particular embodiment, the IRM compound is administered twice.

The IRM compound may be administered before an anticipated exposure to the infectious agent. In some embodiments, the IRM compound is administered once per day for a period before an anticipated exposure to the infectious agent. In certain embodiments, the IRM compound may be administered once per day for two days. In other embodiments, the IRM compound may be administered in a single dose. In some embodiments, at least one dose of the IRM compound is administered 72 hours or less before an anticipated exposure to the infectious agent. In one particular embodiment, for example, the IRM compound is administered in a single dose, about 4 hours prior to exposure to the infectious agent.

In alternative embodiments, the IRM compound may be administered after a suspected or confirmed exposure to the infectious agent. In these embodiments, the IRM compound may be administered once per day for a period after a suspected or actual exposure to the infectious agent. In certain embodiments, the IRM compound may be administered once per day for two days. In other embodiments, the IRM compound may be administered in a single dose. In some embodiments, at least one dose of the IRM compound is administered 72 hours or less after the actual or suspected exposure to the infectious agent. In one particular embodiment, for example, the IRM compound is administered in a single dose, about 4 hours after exposure to the infectious agent.

In other alternative embodiments, the IRM compound may be administered before an anticipated exposure to an infectious agent, and again after the exposure to the infectious agent has, or is suspected to have, occurred.

Subjects

The methods of the present invention may be performed on any suitable subject. Suitable subjects include but are not limited to animals such as but not limited to humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, or cows.

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention. Unless otherwise provided, all percentages are given as w/w%.

The IRM compound used in the examples is N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide, the synthesis of which is described in example 268 of U.S. Ser. No. 10/425,054, filed April 28, 2003.

Example 1

IRM compound was prepared as a 0.375% solution formulation capable of being nasally administered via a spray pump. The formulation vehicle was prepared as follows:

Table 1

Excipient	w/w%
Carboxymethyl cellulose, USP (Spectrum Chemicals and Laboratory Products, Inc., Gardena, CA,)	0.1
Benzalkonium chloride, Ph. Eur. (Fluka, Buchs Switzerland)	0.02
Disodium EDTA, USP (Spectrum Chemicals)	0.1
L-Lactic acid, Purac (Lincolnshire, IL)	1.53
PEG 400, NF (Spectrum Chemicals)	15
1 N NaOH, NF (Spectrum Chemicals)	qs
Water	qs
Total	100.00
pH	4.0

Carboxymethyl cellulose (CMC) was hydrated in water (about 50% of total) for 20 minutes with stirring. The EDTA was added and dissolved. The CMC/EDTA solution was mixed with the benzalkonium chloride to form a CMC/EDTA/BAC solution. Separately, the lactic acid and PEG 400 were mixed with water. For the IRM formulation,

IRM compound was dissolved into the lactic acid/PEG 400 solution. The CMC/EDTA/BAC solution was mixed with lactic acid/PEG 400 solution to prepare the Vehicle formulation. The CMC/EDTA/BAC solution was mixed with lactic acid/PEG 400/IRM solution to prepare the IRM formulation. 1 N NaOH was added, as necessary, to adjust each formulation to a pH of 4.0. Finally, water was added to each formulation to adjust to the final formulation weight.

Example 2

Fisher 344 rats (Charles River Laboratories, Raleigh, NC) were divided into six treatment groups. Rats in each group were infected intranasally with humanized, non-lethal influenza virus. 24 hours after infection, viral titers were measured in nasal lavage fluid and whole lung homogenates. The influenza virus and methods for measuring viral titers are described in Burleson, Gary L., "Influenza Virus Host Resistance Model for Assessment of Immunotoxicity, Immunostimulation, and Antiviral Compounds," *Methods in Immunology* 2:181-202, Wiley-Liss Inc., 1995..

Each of the six treatment groups received a different pre-infection treatment. Rats in each group received the treatment indicated in Table 2. The results are summarized in Figure 1 and Figure 2.

Table 2

Group	Treatment
1	Vehicle formulation (Table 1), 50 µL (25 µL per nare), 1x*
2	Interferon-α (rat recombinant IFN-α, Cat. No. PRP13, Serotec Inc., Raleigh, NC), 10,000 IU, 1x
3	IRM formulation (Table 1), 50 µL (25 µL per nare), 1x
4	Vehicle formulation (Table 1), 50 µL (25 µL per nare), 2x**
5	Interferon-α , 10,000 IU, 2x (Day -1: Product No. RR2030U, Pierce Biotechnology, Inc., Rockford, IL; Day 0: Serotec Inc. Cat. No. PRP13)
6	IRM formulation (Table 1), 50 µL (25 µL per nare), 2x

*1x: one dose of treatment provided four hours before viral infection.

**2x: one dose of treatment 24 hours (Day -1) before viral infection, second treatment four hours before viral infection (Day 0).

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. A method of providing prophylaxis to a subject against an infectious agent comprising topically administering to the respiratory tract of a subject an IRM compound in an amount effective to reduce infection by the agent.

2. The method of claim 1 wherein the IRM compound is administered nasally.

3. The method of claim 1 wherein the IRM compound is administered orally.

4. The method of claim 1 wherein the IRM compound is administered from about 72 hours prior to exposure to the infectious agent to about 72 hours after exposure to the infectious agent.

5. The method of claim 4 wherein the IRM compound is administered prior to and after exposure to the infectious agent.

6. The method of claim 4 wherein the IRM compound is administered prior to but not after exposure to the infectious agent.

7. The method of claim 4 wherein the IRM compound is administered after but not prior to exposure to the infectious agent.

8. The method of claim 4 wherein the IRM compound is administered in from 1 to about 12 doses.

9. The method of claim 8 wherein the IRM compound is administered in from 1 to about 3 doses.

10. The method of claim 9 wherein the IRM compound is administered in 1 dose.

11. The method of claim 10 wherein the infectious agent comprises a virus, a bacterium, a parasite, or a prion.

12. The method of claim 12 wherein the virus is an influenza virus.

5

INFECTION PROPHYLAXIS USING IMMUNE RESPONSE MODIFIER COMPOUNDS

Abstract

The present invention provides methods of providing prophylaxis to a subject against an infectious agent. In general, the methods include topically administering to the respiratory tract of a subject an IRM compound in an amount effective to reduce infection by the agent.

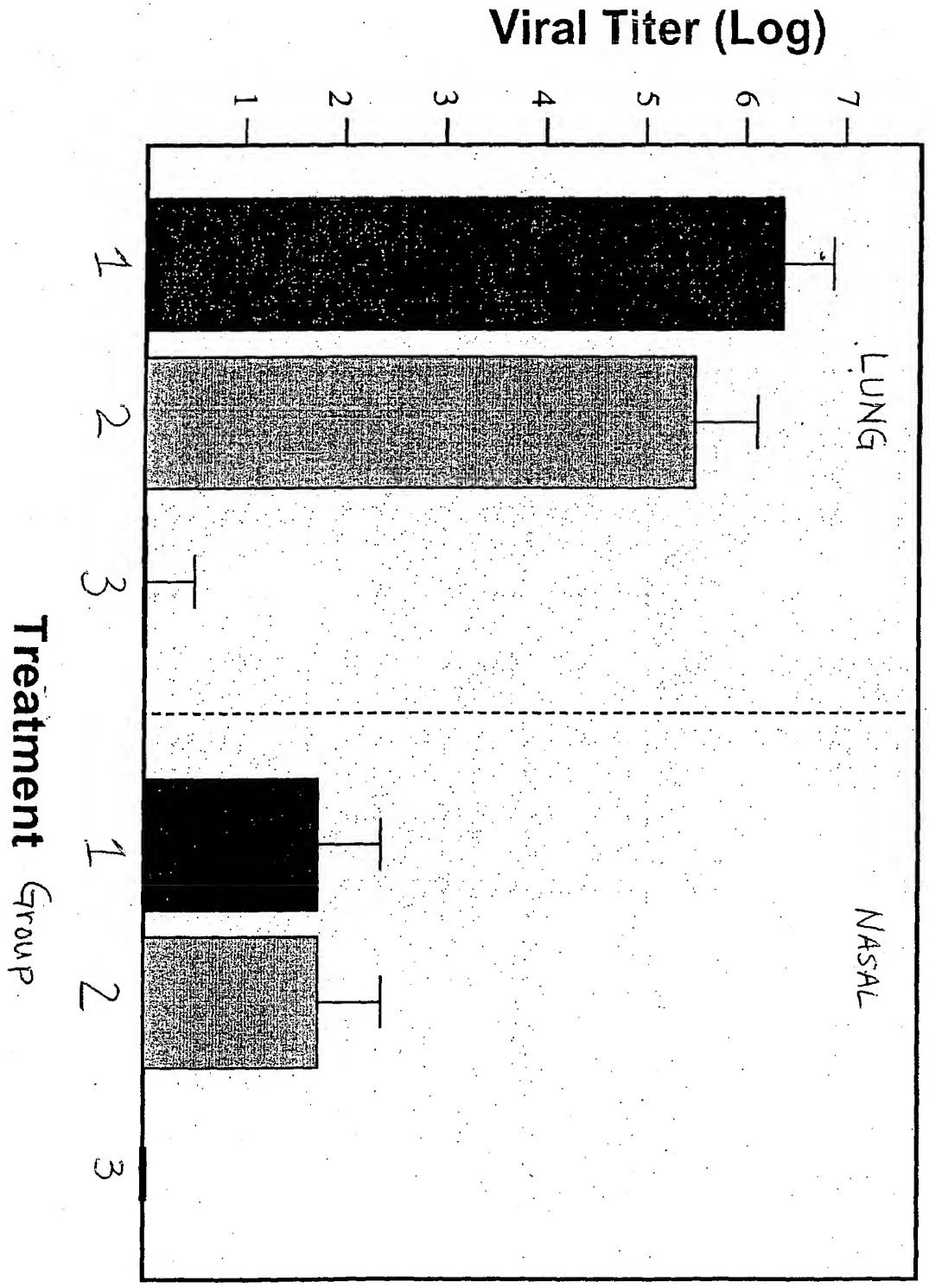

FIG. 1

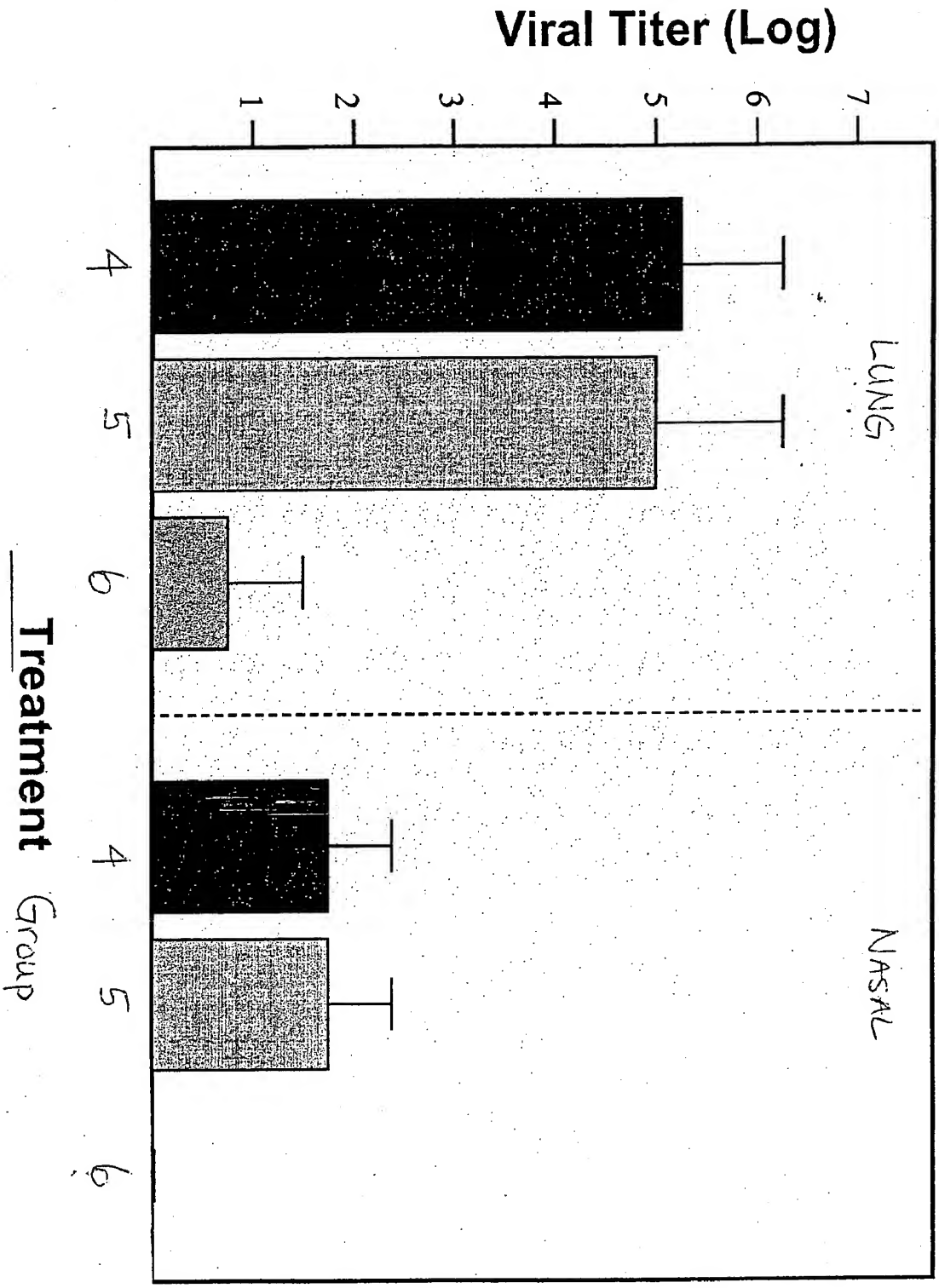

FIG. 2